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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,028	BOENDER, PIET	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-50* is/are pending in the application.

4a) Of the above claim(s) *48-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 27-47, in the reply filed on 7/10/2007 is acknowledged.

2. Claims 48-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/10/2007.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 27-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 27-47 are confusing because claims 27-29 contain improper Markush language, "chosen from the group comprising," and therefore, render the claims unclear.

b. Claims 46-47 are confusing because it is unclear how the claims further limit claim 27. For instance, claim 27 is drawn to a method of generating multiple RNA copies, however, the claims are drawn to the use of the generated copies, and it is therefore unclear how the claim further limits the method of claim 27. While it appears the applicant may have intended dependency on claim 45, it is noted, that it is also unclear how these claims correspond to such a method.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Guillou-Bonnici et al., (US 5,744,308).

Regarding claim 28 and 29, Guillou-Bonnici teaches a method for generating multiple RNA copies comprising the steps of: (a) providing a sample comprising target RNA, wherein said sample is simultaneously contacted with: - a DNA oligonucleotide comprising at its 5' side a promoter sequence recognized by an RNA polymerase, wherein said oligonucleotide further comprises: a target hybridizing sequence (col.7, lines 3-4, 23-29; col.8, lines 42-58, 63-65), which is a predetermined sequence, a modified nucleotide at its 3' terminal end in such a way that extension therefrom is prohibited, wherein said modified nucleotide is chosen from the group comprising nucleotides comprising alkane-diol residues, cordycepins, amino-alkyls, and dideoxynucleotides, at least one chimeric linkage between nucleotides at the 3' end (col.7, lines 58-67); wherein said chimeric linkage may contain at least one phosphorothioate linkage between nucleotides, or a PNA, LNA or GripNA backbone (col.5, lines 55-58; and col.14, lines 27-34, where the polynucleotide sequence can also be modified at the internucleotide bonds), and; an enzyme having Klenow pol I exo (-)

activity [or DNA polymerase activity, claim 29] (col. 9, lines 37-41; col.11, lines 43-54; col.14, lines 51-63); - an enzyme having RNase H activity (col. 9, lines 37-41; col.10, lines 10-12; col.12 line 59; col.14, lines 51-63); an enzyme having RNA polymerase activity (col. 9, lines 37-41; col.12, lines 15-35; col.14, lines 51-63); and - sufficient amounts of nucleotides (col.14, lines 51-63; col.14, lines 51-63); and (b) maintaining the resulting reaction mixture under the appropriate conditions for a sufficient amount of time for the enzymatic processes to take place (see Examples 2-4).

7. Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by McDonough et al. (US 5,766,849).

McDonough teaches a method for generating multiple RNA copies comprising the steps of: (a) providing a sample comprising target RNA (col.3, lines 63-65; col.7, lines 4-5); wherein said sample is simultaneously contacted with: an oligonucleotide comprising at its 5' side a promoter sequence recognized by an RNA polymerase (col.4, lines 37-47; col.6, lines 60-67), wherein said oligonucleotide further comprises: - a target hybridizing sequence, wherein said hybridizing sequence is a predetermined sequence (col.4, lines 6-45; col.6, lines 60-67; Example 1 and 7), a modified nucleotide at its 3' terminal end in such a way that extension therefrom is prohibited, wherein said modified nucleotide is chosen from the group comprising nucleotides comprising alkane-diol residues, cordycepins, amino-alkyls, and dideoxynucleotides (col.4, lines 55-58; col.5, lines 9-15; col.7, lines 7-11; col.8, lines 38-41), at least one chimeric linkage between nucleotides at the 3' end; wherein said chimeric linkage may contain at least

one phosphorothioate linkage between nucleotides, or a PNA, LNA or GripNA backbone (col.5, lines 15-18), and, - an enzyme having DNA polymerase activity (col.5, lines 59-65; col.7, lines 21-40; col.10, lines 54-57); - an enzyme having RNase H activity (col.6, lines 24-38; col.7, lines 21-40; col.8, lines 62-67); - an enzyme having RNA polymerase activity (col.6, lines 1-23; col.7, lines 21-40); and - sufficient amounts of nucleotides; and (b) maintaining the resulting reaction mixture under the appropriate conditions for a sufficient amount of time for the enzymatic processes to take place (col.9, lines 20-42).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 27, 30-34, and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guillou-Bonnici et al., (US 5,744,308), in view of Erlander et al. (US 6,794,141).

The teachings of the primary references are discussed above. Guillou-Bonnici et al. do not discuss the method wherein the target hybridizing sequence is a random sequence [i.e. claim 27].

Erlander et al. teaches a similar method comprising a DNA oligonucleotide as represented in claims 27 and 28 with the exception of a modified nucleotide at the 3' end (col.3, lines 33-37, 50-55; col.8, lines 23-32; col.12, lines 28-34; col.14, lines 1-7).

Erlander also specifically describes the method as entailed in claims 27 and 28 also including a target hybridizing sequence that is a random sequence (see col.8, lines 33-36, and 54-59).

Regarding claim 30-31, Guillou-Bonnici does not discuss the method wherein said target RNA is of eukaryotic, prokaryotic or viral origin, or a mixture thereof [claim 30], or wherein said target RNA is chosen from the group comprising total RNA, mRNA, cRNA, rRNA, tmRNA, asRNA, hnRNA or tRNA, including any combination thereof [claim 31].

The teachings of Erlander are discussed above. Erlander further discusses the method wherein the target RNA is of eukaryotic origin, and the RNA is mRNA (col.6, lines 48-55).

Regarding claim 32, Guillou-Bonnici is silent to whether the predetermined sequence is chosen from the group comprising gene-specific sequences, viral sequences, prokaryotic sequences, mutation-specific sequences, poly-T sequences, genomic sequences and rRNA [claim 32].

The teachings of Erlander are discussed above. Erlander further discusses the method wherein the predetermined sequence is a gene-specific sequence or mutation-specific sequences (col.21, lines 27-32).

Regarding claim 33, Guillou-Bonnici does not discuss the method wherein at least one of the nucleoides, e.g. dNTPs and rNTPs, is provided with a label.

The teachings of Erlander are discussed above. Erlander further discusses the method wherein at least one of the nucleotides are labeled (col.21-22, lines 60-65 and 1-22, respectively).

Regarding claim 34, Guillou-Bonnici does not discuss the method wherein the generated RNA is used as input material for further amplification.

The teachings of Erlander are discussed above. Erlander further discusses the method wherein the generated RNA is used as input material for further amplification (col.20, lines 26-37).

Regarding claim 39-40, Guillou-Bonnici discusses the method wherein said promoter sequence is a T7 promoter sequence and, wherein said RNA polymerase is a T7 RNA polymerase (col.11, lines 65-67; col.12, lines 5-6, 21, 33; col.14, line 57).

Regarding claim 41, Guillou-Bonnici discusses the method wherein said enzyme having DNA polymerase activity is AMV-RT or MMLV-RT (col. 11, lines 55-57).

Regarding claim 42, Guillou-Bonnici teaches the method wherein said enzyme having RNase H activity is E. coli RNase H (col.14, line 63).

Regarding claims 43-44, Guillou-Bonnici does not discuss the method wherein said enzyme having RNase H activity is reverse transcriptase, and wherein said enzyme having RNase H activity is AMV-RT or MMLV-RT.

The teachings of Erlander are discussed above. Erlander further discusses the method wherein said enzyme having RNase H activity is reverse transcriptase, and wherein said enzyme having RNase H activity is AMV-RT or MMLV-RT (col.16, lines 13-16).

Regarding claim 45, Guillou-Bonnici does not discuss a method for determining differences in gene expression in cell samples, comprising the steps of: creating multiple RNA copies of one or more target RNA species according to the method of claim 27, whereby a first pattern of expression is formed from the sample; comparing said first pattern of expression with a predetermined pattern of expression, whereby differences in gene expression are determined.

The teachings of Erlander are discussed above. Erlander also teaches a method for determining differences in gene expression in cell samples, comprising the steps of: creating multiple RNA copies of one or more target RNA species according to the method of claim 27 (with the exception of the oligonucleotide comprising a 3' terminal modified nucleotide), whereby a first pattern of expression is formed from the sample; comparing said first pattern of expression with a predetermined pattern of expression, whereby differences in gene expression are determined (col.21, lines 6-47).

Regarding claims 46-47, Guillou-Bonnici does not teach the method according to claim 27, wherein said multiple RNA copies are used to interrogate a probe array and, wherein said probe array is an oligonucleotide array.

The teachings of Erlander are discussed above, also specifically teaching using said multiple RNA copies to interrogate a probe array and, wherein said probe array is an oligonucleotide array (col.21, lines 6-47).

One of ordinary skill in the art would have been motivated to modify the method of Guillou-Bonnici et al. to use an oligonucleotide that comprises a target hybridizing sequence that is a random sequence because Erlander et al. describe a similar method

and demonstrate the benefits of method incorporating a random target hybridizing sequence in the oligonucleotide in order to amplify target sequences which may be unknown. The skilled artisan would have had a reasonable expectation of success in using a random sequence as the target hybridizing sequence in the method of Guillou-Bonnici et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed random target hybridizing sequence therein.

10. Claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guillou-Bonnici et al., (US 5,744,308), in view of Erlander et al. (US 6,794,141), as applied to claims 27, 30-34, and 39-47 above, and further in view of Van ~~Gent~~ GEMEN (WO 99/43850).

The teachings of the primary reference are discussed above. These references do not discuss the method wherein the generated RNA is contacted with: an RNA ligase, a double stranded nucleic acid complex comprising a double stranded DNA promoter sequence that can be recognized by an RNA polymerase, whereby one strand of said complex has a stretch of RNA attached to the S' end of one of the DNA strands, an enzyme having RNA polymerase activity, and sufficient amounts of dNTPs and rNTPs; wherein the resulting reaction mixture is maintained under the appropriate conditions for a sufficient amount of time for the enzymatic processes to take place [i.e. claim 35-36]. These references also do not discuss the method wherein the generated RNA copies are contacted with poly A polymerase [i.e. claim 37].

Van Gent discusses a similar method as in claim 27, with the exception of the oligonucleotide comprising at least one chimeric linkage between nucleotides at the 3' end (see abstract). Van Gent further discusses the method wherein the generated RNA is contacted with: an RNA ligase, a double stranded nucleic acid complex comprising a double stranded DNA promoter sequence that can be recognized by an RNA polymerase, whereby one strand of said complex has a stretch of RNA attached to the S' end of one of the DNA strands, an enzyme having RNA polymerase activity, and sufficient amounts of dNTPs and rNTPs; wherein the resulting reaction mixture is maintained under the appropriate conditions for a sufficient amount of time for the enzymatic processes to take place (see abstract).

Van Gent also discusses the method wherein the generated RNA copies are contacted with poly A polymerase (see pg.5, lines 1-7).

One of ordinary skill in the art would have been motivated to modify the method of Guillou-Bonnici et al. and Erlander et al. to further react the generated RNA copies with an RNA ligase and a double stranded nucleic acid complex or a Poly A polymerase because Van Gent demonstrates that a further amplification as described in claims 35-36 or 37 can be used after generation of the RNA copies when the amplification does not yield enough copies of RNA and RNA can be amplified further without introducing selectivity by using such a method comprising RNA ligase and the double stranded nucleic acid (pg.4, lines 4-13), or by adding a poly A stretch to the 3' end of the newly synthesized RNA (col.5, lines 1-5). The skilled artisan would have had a reasonable expectation of success in further reacting the generated RNA copies with an RNA ligase

and a double stranded nucleic acid complex or a Poly A polymerase in order to produce a sufficient yield in the method of Guillou-Bonnici et al. and Erlander et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed RNA ligase and a double stranded nucleic acid complex or Poly A Polymerase therein.

11. Claims 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guillou-Bonnici et al., (US 5,744,308), in view of Erlander et al. (US 6,794,141), as applied to claims 27, 30-34, and 39-47 above, and further in view of Serafini et al. (US 6,114,152).

The teachings of the primary references are discussed above. These references do not discuss the method wherein the generated RNA copies are contacted with poly A polymerase [claim 37], or wherein the starting material is simultaneously contacted with a poly A polymerase [claim 38].

Serafini et al. discuss a similar method of claim 27, comprising the same enzymes, and an oligonucleotide comprising a 5' promoter sequence and a 3' target hybridizing sequence with the exception of the oligonucleotide comprising at least one chimeric linkage between nucleotides at the 3' end and comprising one 3' terminal modified nucleotide. Serafini further discusses the method comprising contacting the generated RNA copies with a poly A polymerase (col.4, lines 40-53), as well as simultaneously contacting the starting material with Poly A polymerase (col.2, lines 47-67).

One of ordinary skill in the art would have been motivated to modify the method of Guillou-Bonnici et al. and Erlander et al. to further react the generated RNA copies with a poly A polymerase or simultaneously contact the starting material with a poly A material because Serafini not only describes the benefits of using poly A polymerase in such a manner during a similar method, but demonstrates that it was conventional in the art at the time of the invention to use Poly A polymerase during similar methods. The skilled artisan would have had a reasonable expectation of success in further reacting the generated RNA copies with a poly A polymerase or simultaneously contacting the starting material with a poly A material in the method of Guillou-Bonnici et al. and Erlander et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed Poly A polymerase therein.

12. Claim 27, 28, 30-34, and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonough et al. (US 5,766,849), in view of Erlander et al. (US 6,794,141).

The teachings of the primary reference are discussed above. McDonough does not discuss the method wherein the target hybridizing sequence is a random sequence [i.e. claim 27], nor does he discuss the method wherein the enzyme has Klenow pol I exo (-) activity [i.e. claim 28].

Erlander et al. teaches a similar method comprising a DNA oligonucleotide as represented in claims 27 and 28 with the exception of a modified nucleotide at the 3'

end (col.3, lines 33-37, 50-55; col.8, lines 23-32; col.12, lines 28-34; col.14, lines 1-7). Erlander also specifically describes the method as entailed in claims 27 and 28 also including a target hybridizing sequence that is a random sequence (see col.8, lines 33-36, and 54-59), as well as using an enzyme with Klenow pol I exo (-) activity (see col.15, lines 21-24, 40-43).

Regarding claims 30-32, McDonough teaches the method wherein said target RNA is of eukaryotic, prokaryotic or viral origin, or a mixture thereof [claim 30], wherein said target RNA is chosen from the group comprising total RNA, mRNA, cRNA, rRNA, tmRNA, asRNA, hnRNA or tRNA, including any combination thereof [claim 31], and wherein said predetermined sequence is chosen from the group comprising gene-specific sequences, viral sequences, prokaryotic sequences, mutation-specific sequences, poly-T sequences, genomic sequences and rRNA [claim 32] (see Examples 1 and 7, wherein the target is of bacterial or viral origin, rRNA, and the target hybridizing region is complementary thereto).

Regarding claim 33, although McDonough discusses the oligonucleotide being labeled, she does not discuss the method wherein at least one of the nucleotides, e.g. dNTPs and rNTPs, is provided with a label.

The teachings of Erlander are discussed above. Erlander also discusses the method wherein at least one of the nucleotides are labeled (col.21-22, lines 60-65 and 1-22, respectively).

Regarding claim 34, McDonough discusses the method according to claim 27, wherein the generated RNA is used as input material for further amplification (col.9, lines 1-6).

Regarding claim 39-40, McDonough discusses the method wherein said promoter sequence is a T7 promoter sequence and, wherein said RNA polymerase is a T7 RNA polymerase (col.10, lines 60-67 - col.11, lines 1-3, and Examples, col.12, lines 43-57).

Regarding claim 41, McDonough discusses the method wherein said enzyme having DNA polymerase activity is AMV-RT or MMLV-RT (col.10, lines 53-56).

Regarding claim 42, McDonough teaches the method wherein said enzyme having RNase H activity is E. coli RNase H (col.11, lines 7-11).

Regarding claims 43-44, McDonough teaches the method wherein said enzyme having RNase H activity is reverse transcriptase, and wherein said enzyme having RNase H activity is AMV-RT or MMLV-RT (col.6, lines 25-30; col.11, lines 7-10).

Regarding claim 45, McDonough does not discuss a method for determining differences in gene expression in cell samples, comprising the steps of: creating multiple RNA copies of one or more target RNA species according to the method of claim 27, whereby a first pattern of expression is formed from the sample; comparing said first pattern of expression with a predetermined pattern of expression, whereby differences in gene expression are determined.

The teachings of Erlander are discussed above. Erlander also teaches a method for determining differences in gene expression in cell samples, comprising the steps of:

creating multiple RNA copies of one or more target RNA species according to the method of claim 27 (with the exception of the oligonucleotide comprising a 3' terminal modified nucleotide), whereby a first pattern of expression is formed from the sample; comparing said first pattern of expression with a predetermined pattern of expression, whereby differences in gene expression are determined (col.21, lines 6-47).

Regarding claims 46-47, McDonough does not teach the method according to claim 27, wherein said multiple RNA copies are used to interrogate a probe array and, wherein said probe array is an oligonucleotide array.

The teachings of Erlander are discussed above, also specifically teaching using said multiple RNA copies to interrogate a probe array and, wherein said probe array is an oligonucleotide array (col.21, lines 6-47).

One of ordinary skill in the art would have been motivated to modify the method of McDonough et al. to use an oligonucleotide that comprises a target hybridizing sequence that is a random sequence, or Klenow pol I exo (-) as the DNA polymerase activity because Erlander et al. describe a similar method and demonstrate the benefits of method incorporating a random target hybridizing sequence in the oligonucleotide in order to amplify target sequences which may be unknown, and further demonstrate that it was conventional in the art to use Klenow pol I exo (-) as a DNA polymerase in such methods. The skilled artisan would have had a reasonable expectation of success in using a random sequence as the target hybridizing sequence and Klenow pol I exo (-) as the DNA polymerase activity in the method of McDonough et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry

out the claimed methods and use the claimed random target hybridizing sequence and Klenow pol I exo (-) therein.

13. Claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonough et al. (US 5,766,849), in view of Erlander et al. (US 6,794,141), as applied to claims 27, 28, 30-34, and 39-47 above, and further in view of Van ~~Gent~~ GEMEN (WO 99/43850).

The teachings of the primary reference are discussed above. These references do not discuss the method wherein the generated RNA is contacted with: an RNA ligase, a double stranded nucleic acid complex comprising a double stranded DNA promoter sequence that can be recognized by an RNA polymerase, whereby one strand of said complex has a stretch of RNA attached to the S' end of one of the DNA strands, an enzyme having RNA polymerase activity, and sufficient amounts of dNTPs and rNTPs; wherein the resulting reaction mixture is maintained under the appropriate conditions for a sufficient amount of time for the enzymatic processes to take place [i.e. claim 35-36]. These references also do not discuss the method wherein the generated RNA copies are contacted with poly A polymerase [i.e. claim 37].

Van Gent discusses a similar method as in claim 27, with the exception of the oligonucleotide comprising at least one chimeric linkage between nucleotides at the 3' end (see abstract). Van Gent further discusses the method wherein the generated RNA is contacted with: an RNA ligase, a double stranded nucleic acid complex comprising a double stranded DNA promoter sequence that can be recognized by an RNA polymerase, whereby one strand of said complex has a stretch of RNA attached to the

S' end of one of the DNA strands, an enzyme having RNA polymerase activity, and sufficient amounts of dNTPs and rNTPs; wherein the resulting reaction mixture is maintained under the appropriate conditions for a sufficient amount of time for the enzymatic processes to take place (see abstract).

Van Gent also discusses the method wherein the generated RNA copies are contacted with poly A polymerase (see pg.5, lines 1-7).

One of ordinary skill in the art would have been motivated to modify the method of McDonough et al. and Erlander et al. to further react the generated RNA copies with an RNA ligase and a double stranded nucleic acid complex or a Poly A polymerase because Van Gent demonstrates that a further amplification as described in claims 35-36 or 37 can be used after generation of the RNA copies when the amplification does not yield enough copies of RNA and RNA can be amplified further without introducing selectivity by using such a method comprising RNA ligase and the double stranded nucleic acid (pg.4, lines 4-13), or by adding a poly A stretch to the 3' end of the newly synthesized RNA (col.5, lines 1-5). The skilled artisan would have had a reasonable expectation of success in further reacting the generated RNA copies with an RNA ligase and a double stranded nucleic acid complex or á Poly A polymerase in order to produce a sufficient yield in the method of McDonough et al. and Erlander et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed RNA ligase and a double stranded nucleic acid complex or Poly A Polymerase therein.

14. Claims 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonough et al. (US 5,766,849), in view of Erlander et al. (US 6,794,141), as applied to claims 27, 28, 30-34, and 39-47 above, and further in view of Serafini et al. (US 6,114,152).

The teachings of the primary references are discussed above. These references do not discuss the method wherein the generated RNA copies are contacted with poly A polymerase [claim 37], or wherein the starting material is simultaneously contacted with a poly A polymerase [claim 38].

Serafini et al. discuss a similar method of claim 27, comprising the same enzymes, and an oligonucleotide comprising a 5' promoter sequence and a 3' target hybridizing sequence with the exception of the oligonucleotide comprising at least one chimeric linkage between nucleotides at the 3' end and comprising one 3' terminal modified nucleotide. Serafini further discusses the method comprising contacting the generated RNA copies with a poly A polymerase (col.4, lines 40-53), as well as simultaneously contacting the starting material with Poly A polymerase (col.2, lines 47-67).

One of ordinary skill in the art would have been motivated to modify the method of McDonough et al. and Erlander et al. to further react the generated RNA copies with a poly A polymerase or simultaneously contact the starting material with a poly A material because Serafini not only describes the benefits of using poly A polymerase in such a manner during a similar method, but demonstrates that it was conventional in the art at the time of the invention to use Poly A polymerase during similar methods. The

skilled artisan would have had a reasonable expectation of success in further reacting the generated RNA copies with a poly A polymerase or simultaneously contacting the starting material with a poly A material in the method of McDonough et al. and Erlander et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed Poly A polymerase therein.

Summary

15. No claims are free of the prior art.

16. Aevarsson et al. (US 2004/0058330) is noted as a reference of interest.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

CMEB 8/30/07

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

8/30/07